CASE REPORTS

Auscultatory Sign in Primary Carcinoma of the Liver

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DIAGNOSIS OF primary carcinoma of the liver is difficult to establish before death because signs and symptoms pathognomonic of this malignancy are usually lacking.* The purpose of this article is to characterize a physical sign that apparently is indicative of the presence of a hepatoma. This report describes two cases of hepatocellular carcinoma, each of which was characterized by an abdominal bruit. In both patients, the bruit was heard directly over the enlarged liver, was characteristic of an arteriovenous fistula, and was possibly related, in origin, to the pronounced vascularity of carcinomas of this type.

Reports of Cases

CASE 1.—A 36-year-old man was admitted to the University of California Medical Center for the fifth time 2 November 1965 because of weakness and anemia.

In 1945, he was found on a routine medical examination to be anemic. He remained asymptomatic until 1954, when fatigue developed. He was found to have pancytopenia and a bone marrow aspiration revealed hypoplasia of all marrow elements. Corticosteroid therapy was begun, but numerous blood transfusions (approximately 60 were given from 1954 to 1960) were required to maintain the hematocrit level.

In April 1959, the patient had serum hepatitis, from which he recovered. Splenectomy was performed 2 February 1960. The serum alkaline phosphatase was 10 Shinowara-Jones-Rinehart units (normal, 2 to 6 units).

In February 1965, steroid therapy was discontinued because of the development aseptic necrosis of both femoral heads, and vitamins and fluoxymesterone (Halotestin®) were prescribed. The patient was not icteric, but the liver edge was palpable 2 cm below the right costal margin. A specimen of liver obtained by percutaneous needle biopsy revealed minimal fatty change and hemosiderosis. The alkaline phosphatase was 20 Shinowara-Jones-Rinehart units.

By September 1965 he had become weaker and again required transfusions. Treatment with testosterone enanthate (Delatestryl®), 200 mg intramuscularly weekly, was begun. He was admitted to the Medical Center for the fifth time 2 November 1965 for further evaluation.

On physical examination the patient appeared acutely and chronically ill, although vital signs were within normal limits. His skin was gray, and several spider angiomata and areas of purpura were present. The sclerae were icteric. The lymph nodes were not enlarged, and examination of the heart, lungs and neurological system showed no abnormalities. The liver was palpable 14 cm below the right costal margin and extremely tender. A continuous rough bruit, which was greatly accentuated during late systole, was audible over the central portion of the liver; the sound did not vary with inspiration or changes in the patient's position (Figure 1).

Laboratory tests showed that the platelet count had decreased to 6000 per cu mm. The alkaline phosphatase was 28 Shinowara-Jones-Rinehart units. The serum total bilirubin was 11.2 mg per 100 ml and serum glutamic oxaloacetic transami-

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nase was 268 units. Prothrombin time was 37 per cent and blood ammonia level normal.

Treatment with corticosteroids in large doses (Dexamethasone® 10 mg a day) was begun again. The patient, however, continued to require blood transfusions, the serum bilirubin rose to 17.6 mg per 100 ml, and pancytopenia remained unchanged. On 13 November 1965 he became hypotensive and died.

Postmortem examination revealed hypoplasia of all bone marrow elements, hemosiderosis and a hepatocellular carcinoma. The liver weighed 4600 gm and was diffusely infiltrated by the tumor nodules. Microscopically, the liver parenchyma showed fibrosis, fatty change, chronic inflammatory infiltration and heavy deposition of hemosiderin in both hepatocytes and Kupffer's cells. Death was caused by rupture of a tumor nodule through the liver capsule, followed by massive intraperitoneal hemorrhage. Metastatic lesions were found only in the lungs (microscopically).

CASE 2.—A 60-year-old retired house painter entered San Francisco General Hospital for the second time 14 April 1965 for chemotherapy. He had been admitted previously (23 January 1965) because of increasing abdominal girth and hematemesis. He had a history of chronic alcoholism, and the clinical findings were characteristic of cirrhosis and portal hypertension. The liver was firm, nodular and enlarged, but not tender. Sulfobromophthalein retention was 12 per cent in 45 minutes, the alkaline phosphatase 3.4 Bessey-Lowry units (normal, 0.5 to 3.0 units), and the total serum bilirubin 1.4 mg per 100 ml. Esophageal varices were demonstrated roentgenographically, and a successful spleno-renal shunt was performed 4 March 1965. A biopsy specimen of liver obtained at the time of operation showed the typical changes of portal cirrhosis and a primary hepatoma.

Postoperatively, the patient's condition improved and he was discharged from the hospital. Subsequently, increasing weakness, weight loss, ankle edema and jaundice occurred and he was readmitted to the hospital 14 April 1965.

On physical examination he was observed to be thin and pale and his skin was moderately

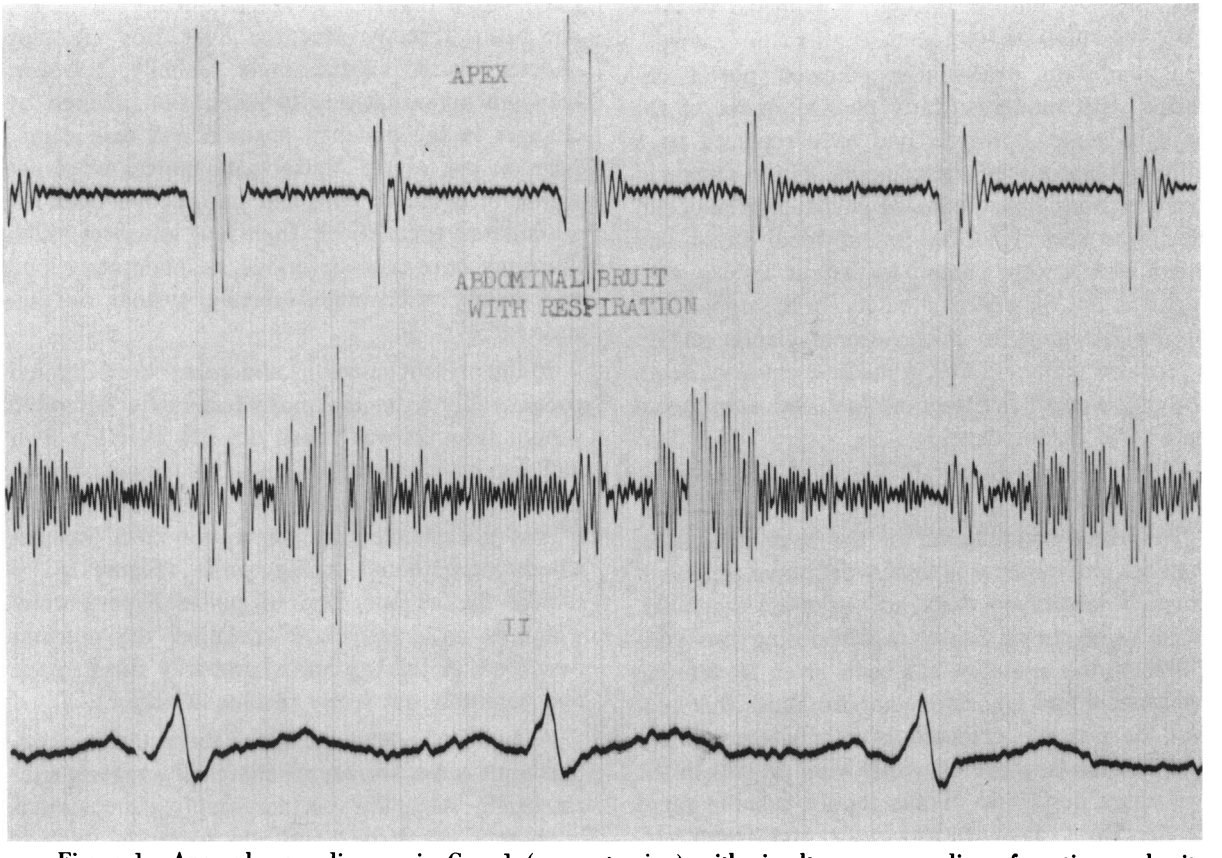

Figure 1.—Apex phonocardiogram in Case 1 (*upper tracing*) with simultaneous recording of continuous bruit over liver (*middle tracing*) and standard lead II of electrocardiogram (*lower tracing*). Note the decided accentuation of the bruit during late systole and the lack of change with respiration.

icteric. The vital signs were within normal limits. The lymph nodes were not enlarged, and no cardiac, pulmonary or neurologic abnormalities were noted. Moderate ascites was present. The liver, which was hard and nodular, was palpable 10 cm below the right costal margin. He had moderate pitting edema of the ankles, slightly greater on the right than on the left. The hematocrit was 27 per cent. Leukocytes numbered 11,800 per cu mm with a normal differential. The platelet count was within normal limits. Alkaline phosphatase was 2.2 Bessey-Lowry units, serum total bilirubin 3.3 mg per 100 ml (conjugated, 2 mg per 100 ml), and the serum glutamic oxaloacetic transaminase 89 units. The prothrombin time was 57 per cent.

The patient was treated with blood transfusions and two five-day courses of 5-fluorouracil, but his condition progressively deteriorated. The alkaline phosphatase increased to 4.3 Bessey-Lowry units and the total serum bilirubin to 9 mg per 100 ml. Hypotension developed and the patient died on 28 May 1965. During the last week of his life a continuous loud harsh murmur, with decided accentuation during systole, was heard directly over the enlarged liver.

Postmostem examination showed portal cirrhosis with moderate fatty change; most of the hepatic tissue, however, had been replaced by a diffuse hepatocellular carcinoma. No evidence of arteriovenous anastomosis or partial arterial occlusion was seen, and the spleno-renal shunt and other vessels were patent. Metastatic lesions were found in the right pleural cavity, in the upper lobe of the left lung, in both adrenal glands and in a thoracic vertebra. The immediate cause of death was rupture of a tumor nodule and subsequent peritoneal hemorrhage.

Discussion

In primary carcinoma of the liver, like most medical and surgical illnesses, definitive treatment depends largely on early and accurate diagnosis. Because of the difficulty in diagnosing this condition, much attention has been given to defining the clinical and laboratory abnormalities that suggest the possible presence of a hepatoma. These manifestations, some of which were present in the two cases described in this report, include rapid deterioration in a patient with preexistent cirrhosis, loss in weight, abdominal pain, progressive enlargement of the liver, increases in the alkaline phosphatase level and the development of ascites.[3,16,27] These abnormalities, however, are not singular to this tumor, and at times such protean and even bizarre signs and symptoms as those associated with an "acute abdomen," pulmonary lesions and pleural effusion, fever of unknown origin, collapsed vertebrae or erythrocytosis may indicate the presence of a primary malignancy of the liver.[2,7,8,14,25,27]

A bruit that develops or is heard over an enlarged liver may also be a manifestation of an occult hepatoma.[2,4,5,12,21] Continuous murmurs, heard during auscultation of the abdomen, have been discussed extensively as to etiology and significance[15,28] since 1833 when Pégot described the bruit he heard over the dilated abdominal veins of an alcoholic soldier.[20] These murmurs have been noted most frequently in patients with cirrhosis, usually in association with portal hypertension, and in the Cruveiler-Baumgarten syndrome, but they also occur in other conditions.[1,4] Usually they are continuous soft murmurs, a venous hum or *"bruit de diable"* first described by Laennec in 1819.[13] Characteristically, they are not heard directly over the liver, nor are they affected by the cardiac cycle. Usually, however, they are accentuated with inspiration, altered by changes in the patient's position and may disappear on use of the Valsalva maneuver or application of pressure with the stethoscope over the auscultated area.[4,9,26,28] In a few instances, such murmurs have been described as moderately loud and mildly accentuated during systole or diastole.[4,18,28,30]

In the present cases, the abdominal bruit differed considerably from the more frequently described venous hum. It was heard directly over the liver and was characteristic of an arteriovenous fistula, that is, it had a machinery-like quality; in addition, it was not affected by respiration and was decidedly accentuated during systole (Figure 1).[6,23] Unlike the venous hum of portal hypertension, which is an extrahepatic murmur, the murmur described in this report is probably intrahepatic and definitely not solely venous in origin.

Although the actual cause of this arteriovenous-like bruit is not known, its character suggests arterial origin. Also, the vascular supply of hepatomas in general is derived entirely from the hepatic artery, thus creating a tissue pattern quite different from that seen in a normal or even a cirrhotic

liver.[21] This distinctive tissue pattern is found typically in the most frequent form of liver carcinoma, the hepatocellular variety,[24] the type present in the two cases described in this report. It is possible that in an enlarging, vascular carcinoma of this type, the arterial blood is frequently shunted into venous channels and occasionally produces a bruit resembling that of an arteriovenous fistula. Alternatively, the bruit might be caused by a partial intrahepatic or extrahepatic arterial obstruction, such as by a tumor nodule. The continuous nature of the murmur heard in the present two cases, however, is evidence against such a mechanism.

Whether this physical sign is a reliable indicator of an underlying hepatoma will require further experience. The findings in the present two cases, however, suggest that the appearance of this type of bruit in a patient with hepatomegaly should alert the physician to the possibility that a primary carcinoma of the liver is present.

Summary

A continuous harsh murmur, characteristic of that produced by an arteriovenous fistula, was audible on abdominal auscultation in two patients with hepatocellular carcinoma. The bruit, unlike the frequently described venous hum, was heard directly over the enlarged liver, was not affected by respiration or changes in position and was greatly accentuated during systole. The present experience suggests that a hepatoma should be suspected in cases in which a continuous arteriovenous-like bruit is heard over an enlarged liver. It is postulated that murmurs of this type may develop as a consequence of the pronounced vascularity characteristic of hepatocellular carcinomas.

REFERENCES

1. Armstrong, E. L., Adams, W. L., Tragerman, L. J., and Townsend, E. W.: The Cruveilhier-Baumgarten syndrome; review of the literature and report of two additional cases, Ann. Int. Med., 16:113-151, 1942.

2. Benner, E. J., and Labby, D. H.: Hepatoma: Clinical experiences with a frequently bizarre tumor, Ann. Int. Med., 54:620-635, 1961.

3. Berman, C.: Primary carcinoma of the liver, Bull. N. Y. Acad. Med., 35:275-292, 1959.

4. Bloom, H. J. G.: Venous hums in hepatic cirrhosis, Brit. Heart J., 12:343-350, 1950.

5. Brunton, T. L.: Some difficulties of diagnosis in hepatic disease, Trans. Med. Soc. London, 19:114-121, 1896.

NOTE: Since this manuscript was prepared, another report (Clain, D., Wartnaby, K., and Sherlock, S.: Abdominal arterial murmurs in liver disease, Lancet, 2:516, 1966) concerning a similar type of abdominal murmur has been published. It appears that this murmur may be heard over the liver not only in patients with primary hepatomas, but also in those with alcoholic "hepatitis" (an entity which should be easily diagnosed by other means).

6. Callander, C. L.: Study of arteriovenous fistula with analysis of 447 cases, Ann. Surg., 71:428-459, 1920.

7. Case Records of the Massachusetts General Hospital (Case 24-1964): New Engl. J. Med., 270:1060-1067, 1964.

8. Case Records of the Massachusetts General Hospital (Case 46-1964): New Engl. J. Med., 271:620-626, 1964.

9. Cheng, T. O., Sutton, G. C., and Sutton, D. C.: Cruveilhier-Baumgarten syndrome; review of literature and report of case, Am. J. Med., 17:143-150, 1954.

10. Gustafson, E. G.: An analysis of 62 cases of primary carcinoma of the liver based on 24,400 necropsies at Bellevue Hospital, Ann. Int. Med., 11:889-900, 1937.

11. Hoyne, R. M., and Kernohan, J. W.: Primary carcinoma of the liver—A study of thirty-one cases, Arch. Int. Med., 79:532-554, 1947.

12. Kay, C. J.: Primary hepatic cancer, Arch. Int. Med., 113:46-53, 1964.

13. Laennec, R. T. H.: A Treatise on Mediate Auscultation and on Diseases of the Lungs and Heart, Edited by T. Herbert, H. Baillière, London, 1846, pp. 532-533.

14. Libre, E. P., and Rodilosso, P. T.: Hepatoma with dysproteinemia and erythrocythemia, Arch. Int. Med., 115:48-52, 1965.

15. Lichtman, S. S.: Diseases of the Liver, Gallbladder, and Bile Ducts, Third edition, Lea & Febiger, Philadelphia, 1953, p. 685.

16. MacDonald, R. A.: Primary carcinoma of the liver—A clinicopathologic study of one hundred eight cases, Arch. Int. Med., 99:266-279, 1957.

17. MacDonald, R. A., and Mallory, G. K.: The natural history of post-necrotic cirrhosis—A study of 221 autopsy cases, Am. J. Med., 24:334-357, 1958.

18. McFadzean, A. J. S., and Gray, J.: Hepatic venous hum in cirrhosis of liver, Lancet, 2:1128-1130, 1953.

19. Patton, R. B., and Horn, R. C.: Primary liver carcinoma—Autopsy study of 60 cases, Cancer, 17:757-768, 1964.

20. Pégot: Tumeur variqueuse avec anomalie du système veineux et persistance de la veine ombilicale; développement des veines sous-cutanées abdominales, Bull. Soc. Anat. Paris, 8:49-57, 1833.

21. Popper, H., and Schaffner, F.: Liver: Structure and Function, First edition. Blakiston Division, McGraw-Hill, New York, 1957, pp. 599 and 602.

22. Sagebiel, R. W., McFarland, R. B., and Taft, E. B.: Primary carcinoma of the liver in relation to cirrhosis, Am. J. Clin. Path., 40:516-520, 1963.

23. Samuels, S. S.: Diagnosis and Treatment of Vascular Disorders, First edition, Williams and Wilkins, Baltimore, 1956.

24. Schiff, L.: Diseases of the Liver, Second edition, Lippincott, Philadelphia, 1963, pp. 708 and 710.

25. Schonfeld, A., Babbott, D., and Gundersen, K.: Hypoglycemia and polycythemia associated with primary hepatoma, New Engl. J. Med., 265:231-233, 1961.

26. Segal, B. L., and Kalman, P.: Bedside diagnosis of heart disease: Analysis of murmurs, Prog. in Cardiovas. Dis., 6:581-607, 1964.

27. Sherlock, S.: Diseases of the Liver and Biliary System. Third edition, Oxford, Blackwell, 1963.

28. Thayer, W. S.: On the presence of a venous hum in the epigastrium in cirrhosis of the liver, Am. J. M. Sc., 141:313-327, 1911.

29. Wilbur, D. L., Wood, D. A., and Willett, F. M.: Primary carcinoma of the liver, Ann. Int. Med., 20:453-485, 1944.

30. Wollaeger, E. E., and Keith, N. M.: Epigastric thrill and murmur in a case of cirrhosis of the liver with general vascular signs of arteriovenous fistula, Proc. Staff Meet. Mayo Cl., 13:33-41, 1938.